REMARKS

Claims 20-27 are pending. All claims are rejected on indefiniteness and enablement grounds. Claim 26 has been cancelled. Claim 20 has been amended to recite the step of culturing myogenic cells to form a composition of cells and does not present new matter because the specification describes culturing cells throughout. See, for example page 23 line 22. New claims 28 to 32 are presented to describe specific embodiments of the invention and do not recite new matter. The recitations of "plastic surgery" and "injection of silicone" found in these claims are supported by the specification on page 22 lines 28 and 31-32, respectively. The recitation of "transverse injection obliquely through myofibers" is supported by the specification throughout, for example on page 25 lines 32-35. Claim 29 is supported by the statement on page 20 lines 29-30, which state that the concentration of LC6SP ranges "from approximately 5uM to about 5mM." Claims 31-32 are supported by statements on page 28, lines 7-10. Reconsideration and allowance are earnestly requested.

The objections and rejections in the office action are discussed below.

Claim Rejections — 35 U.S.C. § 112

All pending claims stand rejected on indefiniteness grounds. The Examiner argues at the top of page 3 that "the meaning of 'cosmetic alterations' cannot be discerned from" general statements regarding facial, breast, and hip augmentation and muscle mass enhancement as described on pages 22-23 of the specification. In response, Applicant argues that the term is self-evident and further described by other statements in the specification. For example, page 22 lines 31-32 states further that cell therapy "could be used in a much more natural way to replace silicone injections." A skilled artisan in this art field knows what silicone injections are and do, and would understand that "cosmetic alterations" means in this explicit context. In this same vein, Applicant has added new claims 28-30 that more particularly state the use of replacing silicone injections.

The specification teaches on page 22, lines 27 to 35 the use of "the cell therapy concept" in a "broader sense" in the field of plastic surgery. The term "cosmetic

appearance of the subject" is interpreted in this context and the means "cosmetic appearance" in the field of plastic surgery. A skilled artisan understands the range of cosmetic appearance change that is possible in the field of plastic surgery and, upon reading this passage, would reach the intended meaning of "such that the cosmetic appearance of the subject is altered."

The Examiner points out that the term "said composition" in claims 20 and 25 lack antecedent basis. In response, applicant has added the phrase "to form a composition of cells" to claim 20. The Examiner respectfully is requested to drop this rejection.

Claim Rejections — 35 U.S.C. § 112

4a The Examiner has asserted an enablement rejection against all claims on page 3 (item 4a) of the Office Action, arguing that "only myoblasts can actually be proliferated in culture." In response, applicant has replaced "proliferated" with "culturing." The new term describes the condition where "myotubes and/or young muscle fibers can be obtained in culture" as stated by the Examiner. Reconsideration and allowance is requested.

4b The Examiner further argues at the top of page 4 (item 4b) that claim 1 is not enabled for humans "as the disclosure only teaches myoblast transfer into mice" and that "in light of the unpredictability of the art, detailed teachings of the claimed invention are required."

Actually, the specification provides much guidance. The inventor has discovered a procedure for making cell therapy work in humans for the first time. The details of the procedure are provided in the specification so that others may follow in the inventor's footsteps.

The specification teaches under the heading "E. MYOBLAST INJECTION METHODS" from the bottom of page 24 through page *25,* a technique to "improve the fusion rate." The specification further states on page 26 lines 9-10 that "the technique of

myoblast delivery is essential for MTT success" and provides comparative results in Figure 6 wherein the inventor found that injection at an oblique angle over a 2 inch distance was "essential" to the success. Details of this experiment are on page *25,* lines 1-10.

The Examiner has overlooked the importance of this "essential" technique. Without wishing to be bound by a particular theory of the invention, the inventor believes that transplantation in a larger human muscle or body part actually provides superior results in comparison to the mouse model because the mouse muscle is too small to get real transverse injection. Proportionately less damage ensues and a greater proportion of cells fuse when a large muscle is injected. Furthermore, unlike the mouse scenerio where the myofiber orientation was relatively unknown "myofiber orientation of different muscle groups have to be well studied by the orthopedic surgeons who administer myoblast injections" and this fact alone allows even greater success in the human than in the mouse. The applicant points out that he studies myofiber orientation to determine transverse injection, as taught by the specification and that he injects more than 10 billion cells (page 12, lines 8 and 33) with 200 transverse injections. In contrast, others who had failed typically have injected only a total of about 600 million cells over 200 different injections, of unknown orientation.

Applicant has emphasized that "various injection methods were tested and compared including injecting diagonally through the myofibers, perpendicular to the myofiber surface, parallel to the myofibers, and at a single site into the muscle" and that the "goal is to achieve maximum cell fusion with the least number of injections." See page 14, lines 3-8. In this context, the number of cells used per injection, about 60 million, and the total used, being in the billions (page 12, lines 8 and 33), as well as techniques of adding chondroitin sulfate to enhance their effect (page 13, lines 31-35) are important.

The specification also teaches, on page p. 20, lines 19-21, the necessity "to inject as pure as possible fractions of myoblasts in MTT without contaminating fibroblasts."

The specification specifically teaches on page 20, lines 29-31 that "LC6SP (ranging from approximately 5 um to about 5mM) in the transfer medium will likely lead to greater

MTT success" and that insulin administration should be important for "formation of myotubes soon after myoblast injections."

The specification also teaches the importance and effect of exercise and physical therapy, and in particular "moderate exercise after innervation of newly formed fibers" as described on page 27 top.

The invention is a pioneering breakthrough and the applicant has ample real data both in the specification and from subsequent work, showing that the procedures taught in the specification work. Applicant further provides evidence of successful results in attached appendix B. This appendix contains a copy of an FDA notice for fast track approval of the claimed method for a phase III study of the invention on a larger scale. This appendix also includes two recent publications that provide data obtained by the claimed methods. Applicant respectfully requests the Examiner to either acknowledge the data possessed by applicant or else provide contrary data showing that the teachings of the specification and the data obtained by applicant according to those teachings are in error. Reconsideration and allowance are earnestly solicited.

4c The Examiner has rejected claim 21 on enablement grounds at the bottom of page 4 (item 4c), arguing that "conventional wisdom teaches that myoblasts only fuse with myoblasts." Applicant responds that the claimed invention does not rely on myogenic cell fusion with adipocytes and that a skilled artisan can find muscle in breast tissue and in a hip.

The Examiner discusses the 1992 writing of DiMaro, as "conventional wisdom" arguing that applicant has a burden to provide "teachings necessary to overcome conventional wisdom." Applicant already has met this burden and has ample data that demonstrates successful use of the procedure taught in the specification (transverse injection after studying fiber orientation, high cell number per injection, and addition of chondroitin sulfate) in non-regenerating muscle. The argument based on the 1992 DiMaro publication is not relevant to the claims anyway, because the claimed method for augmentation of soft tissue injures the muscle. Injection injures muscle. In fact, applicant has learned to

minimize injury to existing muscle tissue to obtain maximum benefit with a large cell population.

Finally, even assuming that the Examiner's idea of the DiMaro teaching is correct, this fact would not mean that the claimed invention is unenabled by the specification. Applicant is not claiming a particular degree to which donor myoblasts contribute to muscle formation. Augmentation does not require 100% contribution of donor myoblasts. Furthermore, the applicant has well studied this problem of how to obtain a high proportion of donor myoblasts to contribute to muscle formation. In fact, the specification provides solutions to the DiMaro problem. These solutions include for example, use of chondroitin sulfate, using massive numbers of cells, surgically implanting myotubes "into the beds of fat and connective tissues dissected and removed by surgeons" (page 28, lines 9 and 10) and culturing of human myoblasts having MHC-negative phonotypes prepared by cytofluorometry. In view of the lack of relevance and the extensive teaching directed to the problem, the Examiner respectfully is requested to withdraw this rejection.

4d The Examiner has rejected claim 20 on enablement grounds in view of Morgan et al. and others that teach "injection of proliferating undifferentiated muscle cells results in the formation of tumors at the site of injection" (page 5 bottom, 4d). However, in most instances of formation of tumors in animals cited by the Examiner, an immuno-compromised animal was used. Thus, the argument does not relate to the claimed invention where non-immune compromised humans are used. The argument further fails because the specification clearly teaches on page 24 lines 3 1-34 that "all clones of myoblasts eventually produce tumors if allowed to proliferate excessively" and that this problem can be avoided by limiting the proliferation to no more than "30 generations." That is, the applicant was aware of this problem and has provided a sufficient solution to it on page 24 of the specification. The Examiner is cordially requested to withdraw this rejection.

4e The Examiner has rejected claim 26 (page 6, 4e) on separate enablement grounds. Applicant has cancelled this claim, mooting the rejection.

Double Patenting

Applicant intends to file a terminal disclaimer in the event that conflicting claims are allowed.

Respectfully submitted,

6/8/99
Date

Marvin A. Motsenbocker
Reg. No. 36,614

FOLEY & LARDNER
3000 K Street, N.W.
Suite 500
Washington, D. C. 20007-5109
(202) 672-5300